

REMARKS

Claims 1-15, 24-46 and 50-52 are pending in this application. Claims 1-15 and 33-46 have been withdrawn from consideration. Claim 24 has been amended to more particularly specify the invention. The amendments are supported throughout the specification; thus no new matter has been added. Applicants are submitting herewith the Rule 132 Declaration of Dr. Michel Schneider, PhD, ("Declaration" or "Schneider Declaration") which explains the claimed invention and the cited references. Dr Schneider is an inventor and an expert in, inter alia, the field of ultrasound contrast agents and the dried formulations used to prepare them.

Rejections Under 35 U.S.C. § 112, 2nd ¶

Applicant thanks the Examiner for having withdrawn the rejection of claims 49 and 51 for indefiniteness.

Rejections Under 35 U.S.C. § 102(b)

Applicant thanks the Examiner for having withdrawn the rejection of claims 24, 28-32 and 50-52 for alleged anticipation by Schneider et al. EP 0554213 ("Schneider").

Rejections Under 35 U.S.C. § 103(a)

The rejection of claims 24-32 and 50-52 under 35 U.S.C. § 103(a) for alleged obviousness over Schneider in view of Hugh D. Van Liew ("Hugh") was maintained. The Examiner states that the requirement that the container is sealed renders claim 24 a product-by-process claim and is insufficient to distinguish the cited references.

Applicants respectfully disagree. As an initial matter claim 24 is not a product-by-process-claim. It is directed to a container comprising a dried material comprising a film forming surfactant and a gas which is present at a pressure lower than atmospheric. The requirement that the container is sealed refers to a property of the container and not to any

process steps. Similarly the statement in claim 24 that the container is for use is preparing a gas containing contrast agent for diagnostic imaging refers does not refer to or incorporate a process step. However, as the use language in the preamble appears to be introducing confusion about what is being claimed, solely to expedite prosecution, Applicants have deleted it.

Thus the currently pending claims are directed to a product, a sealed container comprising: 1) a dried material comprising at least one film forming surfactant; and 2) a gas at a pressure lower than atmospheric pressure. As explained in the specification and in the Schneider Declaration, these containers contain a dry formulation which is a contrast agent precursor. The dry formulation is stored in the container in contact with gas at a pressure below atmospheric pressure. In order to produce a contrast agent, the contents of the container are mixed with an aqueous liquid carrier to produce a suspension of gas-filled microvesicles which may be used as a contrast agent. Declaration, ¶ 8.

Once the aqueous liquid carrier is added to the container, the gas in the container, the microvesicles in the suspension and the surrounding medium produced is necessarily at atmospheric pressure. Declaration, ¶ 9.

By including gas at a reduced pressure in the sealed container, lower amounts of gas can be employed than in similar volume containers including gas at atmospheric pressure. Declaration, ¶ 10. See also US 2005/0025710, paragraphs 0045-0048. Applicants unexpectedly found that notwithstanding the reduced amount of gas in the vial, the microvesicles obtained from reconstitution of the dry formulation in the container show comparable stability characteristics to microvesicles obtained by reconstituting microvesicles from a container including gas at atmospheric pressure, as illustrated in Example 14 and particularly Tables 2 to 5 of the instant application. Declaration, ¶ 11. Applicants also found that the claimed invention resulted in improved consistency and reproducibility in the size of the microvesicles generated

using such precursors independent of the amount of agitational energy applied Declaration , ¶ 12. See also Examples 9-11.

Neither Schneider nor Van Liew , whether alone or combined, teach or suggest the claimed product. In particular, the combined references neither teach nor suggest a sealed container including gas at a pressure lower than atmospheric. Furthermore, even if one were to combine the teachings, the references neither teaches nor suggests that placing dried film forming surfactants in a sealed container with gas at pressure lower than atmospheric permits the use of less gas without sacrificing stability of the suspension prepared using the containers or improves the properties of microvesicle suspensions prepared from such contents. Consequently, even if one were to combine the teachings of Schneider and Van Liew, one would not arrive at the claimed invention.

To the extent Schneider discloses sealed containers it is for storing dry formulations under gas at ambient/atmospheric pressure. See Declaration, ¶ 14. See also Office Action at p. 3 (“Further, Schneider teaches that it is advantageous to store this dry powder under an atmosphere of a gas selected according to the invention (page 4, lines 39+).”) Schneider does not teach or suggest a sealed container with a dried material comprising at least one film forming surfactant and a gas at lower than atmospheric pressure. The only disclosure in Schneider of use gas at pressure lower than atmospheric is as a transient and intermediate step in a process to replace a first gas with a second, desired gas, which is at ambient, not reduced pressure:

For instance, the vesicle suspensions, or preferably precursors thereof (precursors here may mean the materials the microvesicle envelopes are made of, or the materials which, upon agitation with an aqueous carrier liquid, will generate or develop the formation of microbubbles in this liquid), can be exposed to reduced pressure to evacuate the gas to be removed and then the ambient pressure is restored with the desired gas for substitution.

Schneider, p. 4, lines 29-33 (emphasis added) Declaration, ¶ 15. During this replacement process, the container is not sealed as required by the instant claims. Indeed, Schneider makes clear that once the container is sealed, the dried material is at ambient pressure “under an atmosphere of a gas selected according to the invention.” Schneider, p. 4, lines 39-40. Declaration, ¶ 15

All dry formulations in Schneider are stored under gas at atmospheric pressure – there is no suggestion to vary the pressure of the gas used in contrast agent precursor compositions, never mind a suggestion of the advantages of storing compositions under a gas at a pressure lower than atmospheric as in the claimed invention. Declaration, ¶ 14. Indeed, Schneider neither teaches nor suggests the surprising advantages of the claimed invention: that by storing the contrast agent precursor compositions at a reduced pressure, less gas may be used without impacting the stability of the microvesicle suspensions produced from the container or that the size of the microvesicles generated using such precursors is consistently reproducible and independent of the amount of agitational energy applied and that such reconstituted suspensions have increased pressure resistance and thus improved stability in vivo. See e.g. US2005/0025710 at ¶ 0038-0042 and Examples.¹

¹ Applicants note that the pressure difference $DP=P_{25}-P_{75}$, mentioned by the Examiner and the critical pressure, P_c , mentioned in Schneider refer to external pressures applied to suspensions of microvesicles, to evaluate their resistance to said external pressure as a measure of stability. These values have no bearing on the pressure of the gas in a sealed container of the dried formulations that may be used to prepare the microvesicles (or, although irrelevant to the instant claims, on the pressure of the gas inside the microvesicles of the prepared contrast agent).

In sum, as Schneider fails to disclose a sealed container comprising a dried material comprising at least one film forming surfactant and a gas at lower than atmospheric pressure and it fails to teach or suggest the advantages of such containers, the contents therein and the microvesicle suspensions produced therefrom.

The Van Liew article fails to remedy these deficiencies. Like Schneider, the Van Liew article fails to teach or suggest sealed containers including dried materials comprising at least one film-forming surfactant and a gas at a pressure lower than atmospheric pressure. Indeed, Van Liew is directed to the properties of aqueous suspensions of microbubbles and does not even discuss dried formulations used to prepare such suspensions, never mind the containers use to store such dried formulations. Declaration, ¶ 16. Furthermore Van Liew neither teaches nor suggests the advantages of sealed containers including gas at reduced pressure found by the instant inventors. Declaration, ¶ 16. Thus, even if one were to combine the teachings of Schneider with those of Van Liew, the skilled person would not have arrived at the instantly claimed invention, precluding a finding of obviousness.

The Examiner cites Van Liew for the proposition that stabilized microbubbles contain gas at reduced pressure:

The crucial aspect of a structural stabilizer is that it must produce a negative pressure inside the bubbles to counter the tendency for outward diffusion of the gases inside” [sic]. The disclosure is clear in the sense that the negative pressure inside the bubbles should be lowered than the surrounding pressure to help stabilizing the bubbles.

OA at 7 (emphasis added). The Examiner states that based on this disclosure and Schneider one skilled in the art would have prepared microvesicles having pressure lower than atmospheric. See OA at 4 (“It would have been obvious to one of ordinary skill in the art at the time the invention was made to prepare gas microvesicles disclosed by Schneider having lowered

pressure and applying Hugh's knowledge that negative pressure inside the bubble to counter the tendency for outward diffusion of the gases....The skilled artisan would have expectations of success to have a composition for contrast agent in aqueous suspension containing microvesicles useful in imaging.” – emphasis added). As explained in detail below and in the Schneider Declaration, Applicants submit that this is an incorrect (and indeed impossible) interpretation of Van Liew. However, even if one were to assume that the Examiner's interpretation is correct, it fails to render the claims obvious. As discussed, *supra* Applicants invention is directed to a sealed container. Microvesicle suspensions, regardless of the pressure contained in the bubbles, are not claimed. Thus, even if the combination of Schneider and Van Liew suggests suspensions of microvesicles including gas at reduced pressure, that is irrelevant to the claimed subject matter.

Regarding the subject matter that is claimed – a sealed container including a dried material comprising one or more film forming surfactants and a gas at reduced pressure - Van Liew is completely silent and Schneider teaches away (by requiring storage with a gas at atmospheric pressure). Neither teach nor suggest that dried formulations in a sealed container with gas at a pressure lower than atmospheric have any advantages. Thus, the cited references cannot render the claims obvious.

The Van Liew Reference

The Examiner's citation of Van Liew appears to be based on a misinterpretation of the statement on page 2045 col. 2, lines 24 et seq.: “The crucial aspect of a structural stabilizer is that it must **produce a negative pressure inside the bubble to counter the tendency for outward diffusion of the gases inside**, especially to counter the strong positive internal pressure due to surface tension when the bubbles are small” (emphasis added).

The phrase “negative pressure” in Van Liew does not refer to an “absolute” negative pressure (in the sense that the pressure inside the bubble is lower than the pressure in the surrounding medium, i.e. atmospheric pressure), but rather to a pressure which counters (i.e. having an opposite direction) the internal overpressure (with respect to the surrounding pressure) caused by surface tension at the gas-liquid interface. Declaration, ¶ 18.

This becomes clear by reading the subsequent mathematical explanation across page 2046. The presence of the stabilizer is intended to act as a counterpressure (P_T) against the hydrostatic pressure (P_γ) exerted by the surface tension. See col. 2 first paragraph (“A stabilization mechanism exerts a counterpressure (P_T) against the tendency of surface tension and other forces to cause outward diffusion of the bubble’s gaseous contents”). Without the stabilizing layer, the gas contained in the bubble will be forced to diffuse outwardly, because of this hydrostatic pressure. The fact that the counterpressure exerted by the stabilizer is considered by the author a “negative pressure” (opposing the “positive” hydrostatic pressure) is only a matter of mathematical convention, to indicate an opposite direction from the hydrostatic pressure, as inferable from equation 3 at the bottom of page 2046, col. 2. In this equation, the hydrostatic pressure “ P_γ ” appears as a positive value, while the counterpressure “ P_T ”, generated by the stabilizer, is indicated as a negative value. Thus, the “negative” pressure generated by the stabilizer balances the hydrostatic pressure on the bubble, to avoid diffusion of the gas in the liquid – it does not mean that the pressure of the gas inside the bubble is lower than the pressure in the surrounding medium. In fact, the microbubble suspension reaches an equilibrium state where the pressure inside the microbubbles, the surrounding medium and the air above are all at atmospheric pressure. Declaration, ¶ 19.

The Double Patenting Rejections

Claims 24, 28-32 and 50-52 remain rejected for alleged obviousness-type double patenting over US Patent Nos. 6485705, 6403057, 6896875, 6592846, 6613306, 6187288, 6042809, 5911972, 6183725 and 6136293 in view of the Van Liew article.

Applicants respectfully disagree. Like Schneider, the cited patents and applications fail to teach or suggest the claimed sealed containers comprising a dried material and a gas at reduced pressure. In each of the cited patents and applications, any dried formulations used to prepare contrast agents are not stored in the claimed sealed containers with a gas at reduced pressure, instead if these patents disclose sealed containers, they contain dried formulations at atmospheric pressure. Furthermore, none of the cited patents or applications teaches or suggests the advantages of employing gas at reduced pressure in contrast agent precursor compositions first discovered and disclosed in the instant application.

Moreover, as explained above, Van Liew, which neither teaches nor suggests sealed containers including a dried material comprising a film forming surfactant and a gas at pressure lower than atmospheric pressure, fails to remedy this deficiency. It too fails to teach or suggest use of gas at below atmospheric pressure in a container for a dried formulation, never mind the advantages use of such reduced pressure gas See Declaration, ¶ 16

In sum, the cited patents and applications cannot render Applicants claims obvious. Applicants request that the double patenting rejections be withdrawn.

CONCLUSION

Applicants submit that the pending claims are allowable. If any questions remain, Applicants invite the Examiner to contact Applicant's undersigned attorney who would welcome a chance to discuss the claims in a telephonic or in person interview.

No fees are believed due in connection with the filing of this response. However, the Director is hereby authorized to charge any required fees and credit any overpayments to Deposit Account No. 50-2168.

Respectfully submitted,

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By: /M. Caragh Noone/

M. Caragh Noone, Reg. No. 37,197
BRACCO RESEARCH USA Inc.
305 College Road East
Princeton, NJ 08540
(609) 514-2454 (phone)
(609) 514-2446 (fax)